PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Value of pulmonary artery pressure in predicting in-hospital death and one-year mortality after valve replacement surgery in middle and aged patients with rheumatic mitral disease: an observational study
AUTHORS	Jiang, Lei; Wei, Xuebiao; He, Pengcheng; Feng, Du; Liu, Yuanhui; Liu, Jin; Chen, Jiyan; Yu, Danqing; Tan, Ning

VERSION 1 - REVIEW

REVIEWER	Eloi Marijon Inserm, France
REVIEW RETURNED	11-Jan-2017

GENERAL COMMENTS	Jiang et colleagues report very interesting novel findings on how pulmonary pressure may impact mid term FU after heart surgery in the setting of rheumatic heart disease. The paper is nicely written and of clinical interest, references appropriate, and information of significant relevance for medical community to improve patients management. I have only minor points the authors could discuss -Please consider a very general overview on Rheumatic Heart Disease, such as one published in lancet in 2012 since the Introduction - Did the authors consider atrial fibrillation in their multiple logistic approach? - Please state more clearly that only systolic PP is considered.

REVIEWER	Flavio Tarasoutchi - Director of valvular heart disease department InCor -Heart Institute, Sao Pauo Universityl
REVIEW RETURNED	31-Jan-2017

GENERAL COMMENTS	Value of pulmonary artery pressure in predicting in-hospital death and one-year mortality after valve replacement surgery in middle and aged patients with rheumatic mitral disease: an observational study “1639 middle and aged patients diagnosed with rheumatic mitral disease undergoing valve replacement surgery” Comment: The authors do not specify what is the main mitral disease (MR or MS) of their coorte, neither say anything about the severity of the mitral lesion.. they just show how many patients have MS in Table 1..

	"Methods: Included patients were divided into four groups based on the preoperative PAP obtained by echocardiogram: group A (PAP≤30mmHg); group B (30mmHg<PAP≤50mmHg), group C (50mmHg<PAP≤70mmHg) and group D (PAP>70mmHg). The relationship between PAP and in-hospital death and cumulative rate of one-year mortality were evaluated." "Conclusions: PAP could serve as a predictor of postoperative in-hospital and one-year mortality after valve replacement surgery in middle and aged patient with rheumatic mitral disease." "To our best knowledge, this is the first study designed to focus on the value of PAP in deciding the prognosis of middle and aged patients with rheumatic mitral disease." Comment: On "Ghoreishi M, et al. Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation: Implications for timing of surgery. J Thorac Cardiovasc Surg 2011;142:1439-52", the authors show almost exactly what the current paper aimed to study. Their methods: Systolic pulmonary artery pressure (sPAP) was measured before operation in 873 consecutive patients who underwent mitral valve surgery for mitral regurgitation between January 2002 and January 2010. PH was classified as none (sPAP < 40mmHg), mild (40≤sPAP<50mmHg), moderate (50≤sPAP<60mmHg) or severe (sPAP ≥ 60mmHg) and their conclusions: Preoperative sPAP is a powerful predictor of early and late survival after mitral valve operation for mitral regurgitation. Even modest increases in sPAP adversely affect outcomes. Mitral valve operation should be performed before the development of PH show that this 2011 paper has the same purpose as the current one. On the other hand, there were only 8% of rheumatic patients in this 2011 paper, and the sPAP was measure using right heart catheterization in 68% of patients. A similar paper published in 2016, by Yang B, et al, showed the "The Impact of Concomitant Pulmonary Hypertension on Early and Late Outcomes Following Surgery for Mitral Stenosis" and had similar conclusions. Other papers had similar purposes and conclusions: - Thunberg CA, Gaitan BD, Grewal A, Ramakrishna H, Stansbury LG, Grigore AM. Pulmonary hypertension in patients undergoing cardiac surgery: pathophysiology, perioperative management, and outcomes. J Cardiothor Vasc Anesth. 2013;27:551-72. - Magne J, Pibarot P, Sengupta PP, Donal E, Rosenhek R, Lancellotti P. Pulmonary hypertension in valvular disease: a comprehensive review on pathophysiology to therapy from the HAVEC Group. JACC: Cardiovasc Imaging. 2015;8:83-99. - Enter DH, Zaki A, Duncan BF, Kruse J, et al. A contemporary analysis of pulmonary hypertension in patients undergoing mitral valve surgery: Is this a risk factor? J Thorac Cardiovasc Surg 2016;151:1288-99 --> this last one with a different conclusion. What's new in this current work is that 100% of the 1639 patients had rheumatic valve disease, and were older than the usual rheumatic patient.

	--> More comments: This paper Value of pulmonary artery pressure in predicting in-hospital death and one-year mortality after valve replacement surgery in middle and aged patients with rheumatic mitral disease: an observational study, does not present new data, once the last guidelines on valvular heart disease already show that pulmonary arterial pressure is an important independent predictor of morbidity and mortality in patients with mitral valve disease (more than 50mmHg). The way it's written does not clarify it's conclusions and discussions. A key point is the great number of rheumatic patients (1639 patients) followed in this prospective observational study. Besides that, the results are not clear nor meaningful.. If the results suggest that middle or aged patients with PAP level > 52.5 mmHg should not undergo cardiac valve surgery, what's their suggestion on how to treat this patients? In this research the authors followed a lot of patients. The author's discussion is focused on the physiopathology of PAP, not trying to justify the conclusions presented (why do elevated sPAP is associated with poor outcome?). What's the definition of "middle and aged patients" ? They just present the average age of 57±6 years.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Eloi Marijon
Institution and Country: Inserm, France
Please state any competing interests or state 'None declared': None
Please leave your comments for the authors below
Jiang et colleagues report very interesting novel findings on how pulmonary pressure may impact mid term FU after heart surgery in the setting of rheumatic heart disease.
The paper is nicely written and of clinical interest, references appropriate, and information of significant relevance for medical community to improve patients management.
I have only minor points the authors could discuss
-Please consider a very general overview on Rheumatic Heart Disease, such as one published in lancet in 2012 since the Introduction
Response: Thanks for your comments. We systematic reviewed this paper and added it as a references in our study.

- Did the authors consider atrial fibrillation in their multiple logistic approach?
Response: Thanks for your comments. Atrial fibrillation was not put in the multiple logistic analysis because there was no statistical significance in univariate analysis.

- Please state more clearly that only systolic PP is considered.
Response: Thanks for your comments. Due to the value of pulmonary artery dystolic pressure is less than systolic pulmonary pressure in clinical practice, we don't measure it as usual. The pulmonary arterial mean pressure, which could only be measured in pulmonary valve regurgitation, it's not at all clear that whether it can be accurately measured by echocardiography. So, according to these advantages, we only considered about systolic pulmonary pressure.

Reviewer: 2

Reviewer Name: Flavio Tarasoutchi - Director of valvular heart disease department
Institution and Country: InCor -Heart Institute, Sao Pauo Universityl
Please state any competing interests or state 'None declared': none
Please leave your comments for the authors below
Value of pulmonary artery pressure in predicting in-hospital death and one-year mortality after valve replacement surgery in middle and aged patients with rheumatic mitral disease: an observational study
"1639 middle and aged patients diagnosed with rheumatic mitral disease undergoing valve replacement surgery"

Comment:
The authors do not specify what is the main mitral disease (MR or MS) of their coorte, neither say anything about the severity of the mitral lesion. they just show how many patients have MS in Table 1.
Response: Thanks for your comments. MS in table 1 was defined as MVA ≤1.5 cm2. Also the severity of MR (<4cm2, 4-8cm2 and >8cm2) was displayed in table 1.

"Methods: Included patients were divided into four groups based on the preoperative PAP obtained by echocardiogram: group A (PAP≤30mmHg); group B (30mmHg70mmHg). The relationship between PAP and in-hospital death and cumulative rate of one-year mortality were evaluated."
"Conclusions: PAP could serve as a predictor of postoperative in-hospital and one-year mortality after valve replacement surgery in middle and aged patient with rheumatic mitral disease."
"To our best knowledge, this is the first study designed to focus on the value of PAP in deciding the prognosis of middle and aged patients with rheumatic mitral disease."

Comment:
On "Ghoreishi M, et al. Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation: Implications for timing of surgery. J Thorac Cardiovasc Surg 2011;142:1439-52", the authors show almost exactly what the current paper aimed to study.
Their methods: Systolic pulmonary artery pressure (sPAP) was measured before operation in 873 consecutive patients who underwent mitral valve surgery for mitral regurgitation between January 2002 and January 2010. PH was classified as none (sPAP < 40mmHg), mild (40≤sPAP<50mmHg), moderate (50≤sPAP<60mmHg) or severe (sPAP ≥ 60mmHg) and their conclusions: Preoperative sPAP is a powerful predictor of early and late survival after mitral valve operation for mitral regurgitation. Even modest increases in sPAP adversely affect outcomes. Mitral valve operation should be performed before the development of PH show that this 2011 paper has the same purpose as the current one.
On the other hand, there were only 8% of rheumatic patients in this 2011 paper, and the sPAP was measure using right heart catheterization in 68% of patients.
Response: Thanks for your comments. The study published by Ghoreishi et al was remarkable and different with our study. First, there is a focus on patients of rheumatic mitral disease in our study, the pathogenesis and prognosis are different with other valvular heart diseases. In the other hand, PAP was measured by echocardiography in our study, echocardiography is a much more convenient and noninvasive approach than right-side heart catheterization.

A similar paper published in 2016, by Yang B, et al, showed the "The Impact of Concomitant Pulmonary Hypertension on Early and Late Outcomes Following Surgery for Mitral Stenosis" and had similar conclusions.
Response: Thanks for your comments. In this great study, the pulmonary pressure was also measure by right-side heart catheterization, as we stated above, the echocardiography used in our study is more convenient and noninvasive, and this study just focus on MS.

Other papers had similar purposes and conclusions:

- Thunberg CA, Gaitan BD, Grewal A, Ramakrishna H, Stansbury LG, Grigore AM. Pulmonary hypertension in patients undergoing cardiac surgery: pathophysiology, perioperative management, and outcomes. J Cardiothor Vasc Anesth. 2013;27:551-72 .
- Magne J, Pibarot P, Sengupta PP, Donal E, Rosenhek R, Lancellotti P. Pulmonary hypertension in valvular disease: a comprehensive review on pathophysiology to therapy from the HAVEC Group. JACC: Cardiovasc Imaging. 2015;8:83-99.
Response: Thanks for your comments. These are outstanding review articles in the similar field, we read them when we were writing the manuscript. We benefit a lot from them and add them as a references in our study.

- Enter DH, Zaki A, Duncan BF, Kruse J, et al. A contemporary analysis of pulmonary hypertension in patients undergoing mitral valve surgery: Is this a risk factor? J Thorac Cardiovasc Surg 2016;151:1288-99 --> this last one with a different conclusion.
Response: Thanks for your comments. We systematically review this paper and find that PASP in this study was obtained by echocardiography or RHC, without recording
the method in their database. Whether the conclusion was suitable for PAP measured only by echocardiography was unclear. Another different from our study was the population included. RHD is still as a major health problem in developing countries. To identify the high risk factor(s) for poor outcomes remains urgent and important.

What's new in this current work is that 100% of the 1639 patients had rheumatic valve disease, and were older than the usual rheumatic patient.

--> More comments:
This paper Value of pulmonary artery pressure in predicting in-hospital death and one-year mortality after valve replacement surgery in middle and aged patients with rheumatic mitral disease: an observational study, does not present new data, once the last guidelines on valvular heart disease already show that pulmonary arterial pressure is an important independent predictor of morbidity and mortality in patients with mitral valve disease (more than 50mmHg).
Response: Thanks for your comments. We systematically review the last guidelines on valvular heart disease. In 2014 AHA/ACC guideline, PASP approaching 50 mm Hg as a risk predictor was only stated in patients with MR. Whether is suitable for MS is unknown.
In 2012 ESC guideline, pulmonary hypertension was considered as an important predictor of postoperative outcome for patients with MR or MS. However, the clear cut-off of PAP was not detailed.
In Euro score, PAP more than 50mmHg was a risk factor for patients undergoing a heart operation (not merely mitral valve disease).
Approximately 50% of RHD affects mitral valve, so it is feasible to conduct this study to explore the effect of PAP on prognosis in middle and aged patients with rheumatic mitral disease, these patients need more attention and care.

The way it's written does not clarify it's conclusions and discussions.
A key point is the great number of rheumatic patients (1639 patients) followed in this prospective observational study.
Besides that, the results are not clear nor meaningful. If the results suggest that middle or aged patients with PAP level > 52.5 mmHg should not undergo cardiac valve surgery, what's their suggestion on how to treat this patients? In this research the authors followed a lot of patients.
Response: Thanks for your comments. This is a retrospective analysis based on prospectively collected data. No intervention was set in our study. The result shown that the cut-off of PAP>52.5mmHg can be suitable for risk assessment in middle and aged patients with rheumatic mitral disease. This may tell us an idea that pulmonary hypertension may be a potential therapeutic target in valve replacement surgery of RHD. A future randomized trial is warranted to confirm whether

decreasing PAP by drugs below the cut-off point indicated in our study would lead to a better outcome.

The author's discussion is focused on the physiopathology of PAP, not trying to justify the conclusions presented (why do elevated sPAP is associated with poor outcome?).
Response: Thanks for your comments. RHD combined with pulmonary hypertension induced pathological changes of pulmonary vessels, since the progression of PH usually leads to the increased right cardiac afterload and later right ventricular hypertrophy (RVH) and heart failure. Previous study has proved that right ventricular dysfunction was associated with poor outcomes. [Circulation. 2013 Apr 16;127(15):1597-608.]
Due to the severe pulmonary vascular wall remodeling, the morphological change of pulmonary vessel wall is irreversible at later stage when patients receiving surgery and the pulmonary artery stress could persist and exceed the systemic arterial blood pressure before operation, the right cardiac afterload would be further aggravated after operation which may lead to low cardiac output syndrome. [Heart 2001;86:715-721; Am J Cardiol 2015;115:1435-1442] Therefore, the postoperative mortality was still high in patient with higher PAP.

What's the definition of "middle and aged patients" ? They just present the average age of 57±6 years.
Response: Thanks for your comments. There is no unified standard for middle patients in the countries of the world. In china, people older than 40 is considered as middle aged. The age range of patients included in our study is from 40 to 81.

VERSION 2 – REVIEW

REVIEWER	Eloi Marijon Inserm, France
REVIEW RETURNED	24-Feb-2017

GENERAL COMMENTS	Good revision

REVIEWER	Flavio Tarasoutchi Flavio Tarasoutchi - Director of valvular heart disease department Institution and Country: InCor -Heart Institute, Sao Paulo University
REVIEW RETURNED	02-Mar-2017

GENERAL COMMENTS	The answers the authors gave me satisfied my questions. With them in my oppinion, the article became completed.